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Predicting Biological Effect as a Function of the Chemical Structure and the Primary Physical and Chemical Properties of Organic Compounds

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The dependence of biological parameters on chemical structure was studied for a series of compounds with similar chemical structures. Computational formulas were developed on the basis of correlation and regression analysis. These formulas make it possible to predict the biological effect thresholds for a great number of organic compounds on the basis of their primary physical and chemical properties.

Introduction

In recent years extensive information has been accumulated in the U.S.S.R. on the comparative toxicity of substances belonging to various chemical classes and maximum permissible amounts of harmful substances in the air in a working environment, taking into account their chemical structures and physical and chemical properties.

At the A. N. Sysin Institute of General and Communal Hygiene of the Academy of Medical Sciences of the USSR a study was conducted of the relationship of the biological activity of 25 compounds with related chemical structures (nitro, amino, chloro, methyl, and oxy derivatives of benzene) and their chemical structure. It was then possible, by computation by correlative and regression analysis, to predict the approximate thresholds of biological activity for organic substances in the atmosphere based on their chemical structure and principal physical and chemical properties.

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The study consisted of three successive stages: experimental determination of reflex action thresholds (determination of the nonspecific odor thresholds and effect of the subsensory concentration thresholds on the electrical activity of the human brain) and the dependence of these thresholds on chemical structure and physical and chemical properties; development of computation formulas which make it possible to predict the biologic parameters of the studied atmospheric pollutants without long-term experimental study; and comparison of the experimental and computed parameters of the biological effects of atmospheric pollutants.

Standards for atmospheric pollutants were based mainly on the study of the reflex reactions of organisms determined by the odor threshold, the effect of chemicals on changes in the darkness adaptation curve, and on the bioelectrical activity of the cortex of the human brain.

Of the 138 hygienic standards for atmospheric pollutants presently in effect in the U.S.S.R., most (14) deal with materials derived from benzene and distinguished by varying substituents on the benzene ring. The first attempt to evaluate the

biological activity thresholds for these compounds was done with benzene derivatives.

Results and Discussion

Nitro substitution was found to have a greater effect on the value of odor threshold concentrations when introduced on a benzene ring than did amino, chlorine, or methyl substituents.

If we take the odor threshold concentration of benzene to be 1.0, then substitution on the benzene ring of one nitro group reduces the concentration required for the odor threshold of corresponding benzene derivatives substitution 153 times, substitution by amino groups produced a 7.5-fold reduction, chlorine, 6.8-fold, and methyl, 1.8-fold.

Odor concentration thresholds of substances are reduced further if, in addition to a nitro group, an amino group or one or two chlorine groups or one methyl group are introduced into the benzene ring.

Methylation of aniline (introduction of one, two, or and three methyl groups) affects reduction of odor thresholds of substances to a larger degree than does chlorination (introduction of one or two chlorine groups). In all cases, the position at which substituents are introduced does not substantially affect odor thresholds of the benzene derivatives investigates.

If we take the odor threshold level of aniline to be 1.0, then introduction of one chlorine group onto a benzene ring in addition to an amino group reduces the level of the odor threshold of the new substances 5 to 10 times, two chlorine group reduce it 8 times, one nitro group 20 times, etc.

Inhalation studies with subsensory concentrations showed that the introduction of a chlorine group on a benzene ring already bearing a nitro substituent results in an insignificant increase of the reflex effect of the compound. The effect is increased, however, with the introduction of one or two chlorine groups to amino substituted benzene.

Electroencephalographic studies of subsensory concentrations of benzene derivatives showed the same relationship as in the determination of their odor thresholds.

On the basis of the empirically determined data, formulas were derived for computation of odor thresholds and electroencephalographic thresholds for other unstudied benzene derivatives [eq. (1)]:

$$BA_N = \frac{\sum_{i=1}^{K} (1/M_i) C_i + \sum_{j=1}^{K} C_j}{abn} \qquad n = 1,2,\ldots\infty \qquad (1)$$

In eq. (1) BA_N denotes the biological activity of the threshold concentrations of N benzene derivatives related to odor and electroencephalography (mg/m^3); C_i is the highest concentration (mg/m^3) for odor or electroencephalographic thresholds established experimentally, taking into account substituents in the molecule of organic compound of the given chemical series; C_j is the lowest concentrations (mg/m^3) for odor or electroencephalographic thresholds established experimentally, taking into account substituents in the same molecule; m_i is a multiplicity factor in excess of high concentrations of principal substituents to low ones (established on the basis of experimental data for principal substituents in the benzene ring: NO_2, OH, NH_2, Cl, CH_3; a is a coefficient characterizing the biological activity of compounds established experimentally, taking into account substituents in the benzene ring; b is a coefficient considering positional isomerism of the substituents in a compound; and n is the number of substituents in the benzene ring (values higher than presented coefficients are based on experimental data).

In accordance with eq. (1) odor and electroencephalographic thresholds were determined for 23 benzene derivatives and compared with experimentally established reflect effect thresholds for the same substances. A statistically highly positive correlation was obtained in computing the odor thresholds in accordance with chemical structure. The difference between the experimental and computed values is 1.2 to 2 times.

By using eq. (1) we calculated the reflex action threshold of 50 new industrial benzene derivatives which do not have experimentally determined standards.

Calculating the reflex action threshold of benzene derivatives from basic physical and chemical properties of the substances is a second possible way of predicting the thresholds.

In studying the correlation dependence of the biological activity thresholds of the 25 benzene derivatives studied on various physicochemical indices, it was shown that the threshold levels of the nonspecific odors of substances are related directly to the values of elasticity ($r = 0.87$; $m_r = 0.057$; $n = 19$, density ($r = 0.56$; $m_r = 0.14$; $n = 24$), heat of formation ($r = 0.66$; $m_r = 0.178$; $n = 10$) and inversely to molecular weight ($r = 0.45$; $m_r = 0.16$; $n = 24$), boiling point ($r = 0.72$; $m_r = 0.098$; $n = 24$), refractive index at 20°C ($r = 0.61$; $m_r = 0.17$; $n = 13$), molecular refraction ($r = 0.68$, $m_r = 0.18$; $n = 13$), surface tension ($r = -0.69$; $m_r = 0.166$, $n = 10$), dipolar moment ($r = 0.50$; $m_r = 0.16$; $n = 22$), coefficient of viscosity ($r = -0.454$, $m_r = 0.3$; $n = 6$),

heat capacity ($r = -0.55$; $m_r = 0.22$; $n = 10$) and melting point ($r = -0.41$; $m_r = 0.17$; $n = 24$).

In those cases where only a satisfactory correlation was obtained, we tend to explain this as due to the small number of compounds studied and the particular lack of those parameters of interest to us in chemical reference books.

Computational formulas which make it possible to predict the reflex action thresholds not only for benzene derivatives, but also for many organic substances of various homologous series based on their molecular weight and boiling point were derived.

An equation for computing the odor threshold of organic substances according to molecular weight in the range 30–300 was derived [eq. (2)].

$$\log y = -6.51 \log x + 12.15 \qquad (2)$$

Here y is the odor threshold concentration (in mg/m^3) and x is the molecular weight value for the given compound.

The following corrections k must be considered in calculating $\log y$: $k = +1.0$ for molecular weight 160.1–260.0; $k = +2.0$ for molecular weight 260.1–300.0; $k = +3.0$ for molecular weight > 300; $k = -1.0$ for molecular weight 74.0–30.0.

An equation derived for calculating the odor threshold of organic substances with boiling points in the range 37–315°C is given in eq. (3):

$$\log y = -6.4 \log x + 13.2 \qquad (3)$$

Here y is the odor threshold concentration (in mg/m^3) and x is the boiling point of the given substance (in °C).

The following corrections k must be considered in calculating $\log y$: $k = +1.0$ for boiling point $>$ 260.0°C; $k = -1.0$ for boiling point 75.0–65.1°C; $k = -2.0$ for boiling point 65.0–60.0°C; $k = -3.0$ for boiling point 59.0–37.0°C.

The equation for calculating the electroencephalographic threshold of organic compounds with boiling points in the range 78–270°C is given as eq. (4).

$$\log y = -5.3 \log x + 10.76 \qquad (4)$$

Here y is the electroencephalographic threshold (in mg/m^3) and x is the boiling point of (in °C).

Equation (4) was verified on benzene derivatives ($r = 0.953$; $m_r = 0.021$).

The difference between experimental and computed reflex action thresholds in accordance with eqs. (2)–(4) did not exceed 3 to 5, and in individual cases 7 times. The accuracy of the computed values of the reflex action thresholds may in the future be increased with accumulation of experimental data for other compounds which in turn will make it possible to make correction limits k more precise.

The coefficient of correlation of the experimental and computed odor thresholds for 25 benzene derivatives was found to be 0.884 ($m_r = 0.044$) for eq. (2) and 0.914 ($m_r = 0.033$) for eq. (3).

Good correlation was established between the experimental odor thresholds for 70 organic substances of various chemical series and the computed odor thresholds with respect to molecular weight [eq. (2)] and boiling point [eq. (3)]. The coefficients of correlation were 0.51 and 0.75, respectively, and the error was 0.089 and 0.055, respectively.

The odor thresholds of organic compounds with molecular weights from 30 to 330 may be made calculated by eq. (2). The odor thresholds of organic substances with boiling points from 37 to 315°C may be calculated by use of eq. (3) on taking into consideration in both cases the recommended corrections in computing logarithms. In obtaining results in eqs. (2) and (3) simultaneously, it is recommended that average values be used for the approximate values of the odor thresholds.

Computation of the electroencephalographic thresholds for organic compounds with boiling points from 78 to 270°C may be made by eq. (4) or from the odor threshold by the relationship,

$$\text{Electroencephalographic threshold} = \text{odor threshold}/2.5 \qquad (5)$$

or for compounds of the same chemical series by the relationship

$$\text{Electroencephalographic threshold} = \text{odor threshold}/2.0 \qquad (6)$$

Coefficients given in eqs. (5) and (6) were derived by us on the basis of processing experimental research data for all organic substances included in sanitary legislation ($n = 87$; $M_{av} = 2.45$; $m = 0.17$) and 17 benzene derivatives ($M_{av} = 2.16$; $m = 0.278$).

Comparison of experimental and computed reflex action thresholds of organic substances with respect to chemical structure, molecular weight, and boiling point will make it possible to evaluate the conformity of experimental threshold values to computed ones.

Determination of the dependence of the biological activity of atmospheric pollutants on their various physical and chemical properties will make

it possible in the future on the basis of correlative and regressive analysis to arrive at broad prediction not only of the approximate biological effect thresholds for substances but also of the tentative maximum permissible concentrations for substances in the ambient air from their chemical structures without conducting long-term experimental studies.